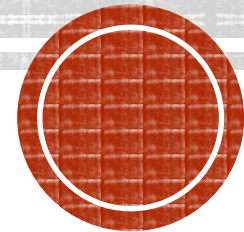




EMPIRICAL
Improving Treatment for Pneumonia
in HIV-infected Infants

EMPIRICAL PROJECT




This project is part of the
EDCTP2 programme supported
by the European Union

In response to limited focus globally on Pediatric AHD, in 2020 the World Health Organization (WHO) released the STOP AIDS package of care for children and adolescents with AHD

↓ In July 2020, the WHO released a [technical brief](#) on a package of care for children and adolescents with advanced disease to lay a groundwork for proper care for young people living with AIDS

↓ PEPFAR's 2021 COP Guidance stated the need to incorporate this (2020 WHO STOP AIDS) package of AHD interventions into pediatric HIV programs

↓ Global Fund's Information Note (July 2022) identified the provision of a package of care that reduces mortality in individuals with advanced HIV disease in adults and children as a priority intervention



TECHNICAL BRIEF – JULY 2020
PACKAGE OF CARE FOR CHILDREN AND ADOLESCENTS WITH ADVANCED HIV DISEASE: STOP AIDS

World Health Organization, UNICEF, UNAIDS, and UNFPA logos are visible at the bottom.

Box 1. Screen, treat, optimize and prevent AIDS

Screen*

- Screen for TB using a chest algorithm¹ followed by X-ray when indicated and if available
- Use the following diagnostic tests to confirm TB as applicable:
 - Rapid molecular diagnostic (Xpert® MTB/RIF or Xpert® MTB/RIF Ultra)² or other laboratory sample if relevant
 - Standardized sputum smear microscopy³ if TB not ruled out

Optimize

- Confirm or detect or detect rifampicin resistance followed by further purchase of products as appropriate
- Medication:
 - Weight for height
 - Height for age
 - Malnutrition assessment according to WHO guidelines

Prevent

- TB, severe pneumonia, severe bacterial infections, opportunistic infections according to WHO guidelines
- Optimize
 - Rapid antiretroviral therapy start within seven days with optimal antiretroviral therapy counseling

Prevent


- Bacterial infections and Pneumocystis pneumonia
 - Co-trimoxazole prophylaxis
- TB
 - TB preventive treatment
 - Opportunistic infections among adolescents
 - Herpesvirus perinatal therapy
- Medication
 - Prophylaxis of toxoplasmosis
 - Herpesvirus prophylaxis
 - Mucocutaneous

* Screening of children and adolescents should be done in the following order: 1. TB, 2. Severe pneumonia, 3. Severe bacterial infections, 4. Opportunistic infections.

Table 1. Screening, diagnosis and prevention components of the package of care for children and adolescents with advanced HIV disease

Intervention	Component	<5 years	5-9 years	10-19 years
Screening and diagnosis	Screen for TB using chest algorithm followed by X-ray when indicated and if available	Yes	Yes	Yes
	Xpert® MTB/RIF or Xpert® MTB/RIF Ultra when available	Yes	Yes	Yes
	Standardized sputum smear microscopy or other laboratory sample if relevant	Yes	Yes	Yes
Prevention, prophylaxis and antiretroviral treatment	Co-trimoxazole	Yes	Yes	Yes
	TB preventive treatment	Yes	Yes	Yes
	Herpesvirus perinatal therapy	Yes	Yes	Yes

PEPFAR 2021 Country and Regional Operational Plan (COP/ROP) Guidance for all PEPFAR Countries




Information Note
HIV Information Note
Allocation Period 2023-2025
Date published: 29 July 2022



The guidance is now in place from WHO, donors and partners to enable countries to adopt, implement and scale up interventions to reduce AHD related mortality in children and adolescents

Ana Moore





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- **Empirical** use of valganciclovir and tuberculosis treatment in chest indrawing and severe pneumonia in HIV-infected infants: a randomized controlled clinical trial



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Improving Treatment for Pneumonia
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Clinical trials to reduce health inequities in pregnant women, newborns and children

Status:	Closed
Type of action:	Research and Innovation Action (RIA)
Call budget:	€38.23 M
Funding level:	Up to 100% of eligible costs
Stage 1 Open date:	4 July 2017, 17:00
Stage 1 Close date:	13 October 2017, 17:00
Stage 2 Open date:	22 December 2017, 17:00
Stage 2 Close date:	14 March 2018, 17:00

[Go to EDCTPgrants](#)

Expected number of grants: 5-10

Call identifier: RIA2017MC



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Hypothesis

- Empirical treatment with valganciclovir and treatment against TB will improve survival in HIV infected infants with severe pneumonia.





Primary Aims

1.1. To compare empirical treatment against CMV with valganciclovir (powder for solution, 50 mg/mL) versus no treatment

valganciclovir will reduce 15-day mortality

1.2. To compare empirical treatment against TB versus no treatment

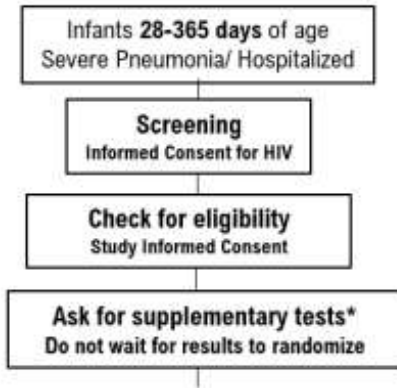
TB treatment will reduce 1-year mortality





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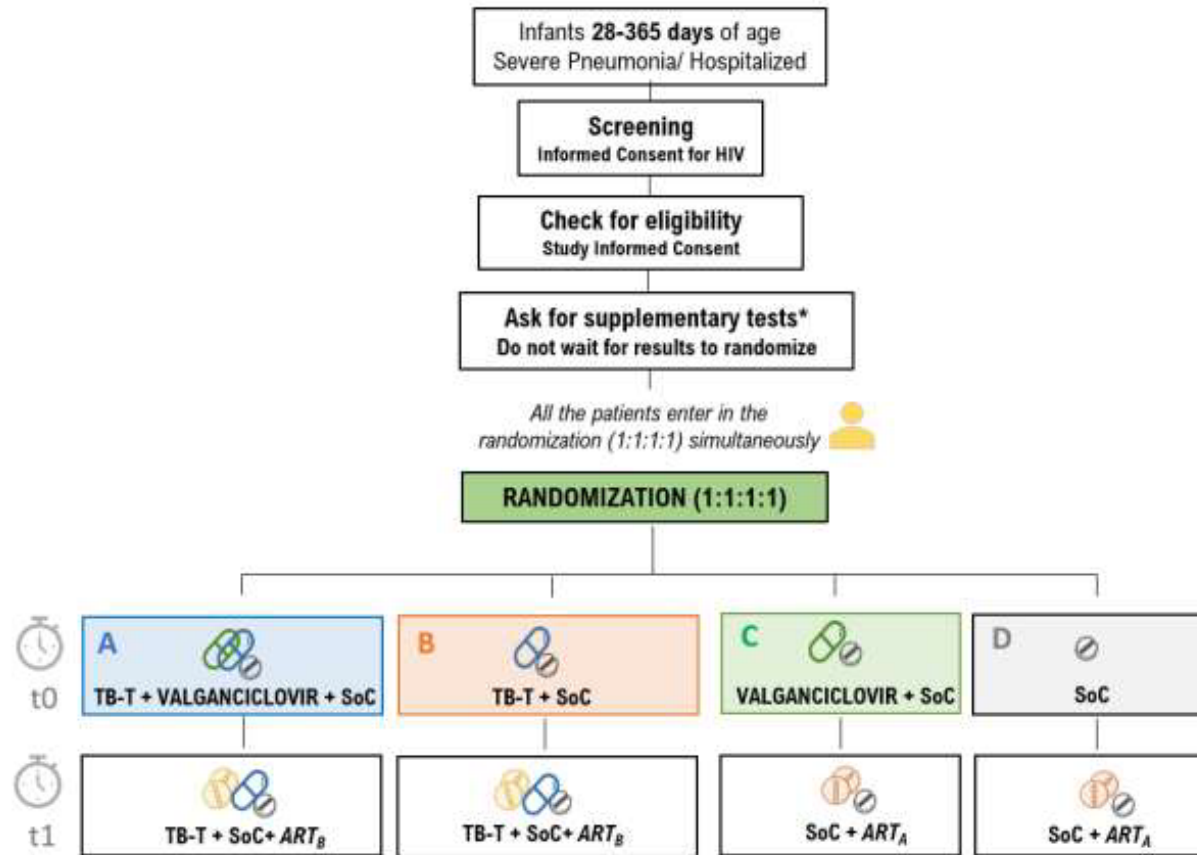
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Improving Treatment for Pneumonia
in HIV-infected Infants

- ❑ Phase II-III, open label, factorial trial
- ❑ 6 countries, 20 hospitals.
- ❑ Population:
 - 30 d-365 d
 - HIV+
 - Severe pneumonia
- ❑ Recruited **518**/600 children expected
- ❑ Finish recruitment January 31st 2024



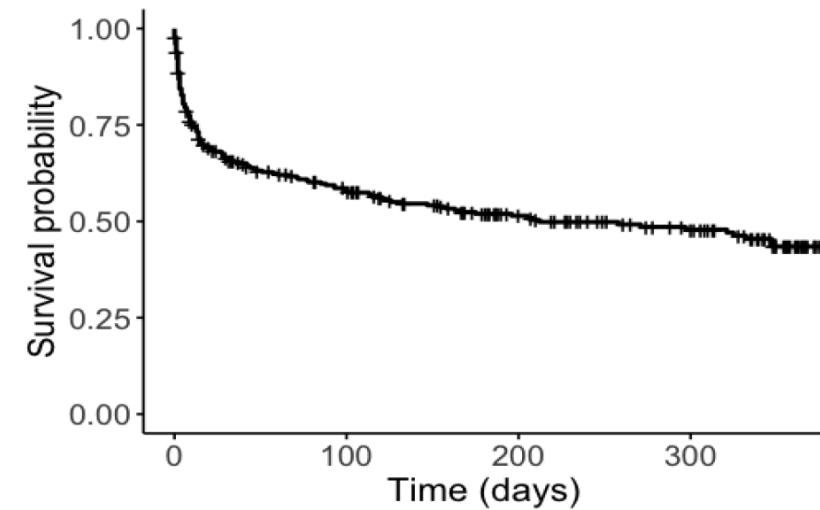
High Mortality in African Infants Hospitalized with Severe Pneumonia and Advanced HIV #810

Alfeu Passanduca¹, W. Chris Buck^{1,2*}, Alfredo Tagarro³, Victor Musiime⁴, Hilda Angela Mujuru⁵, Chishala Chabala⁶, Lola Madrid³, Sara Domínguez-Rodríguez³, Pui-Ying Iroh Tam⁷, Tisungane Mvalo⁶, Justina Magalhaes-Bramugy⁹, Raoul Moh¹⁰, Álvaro Ballesteros³, Cinta Moraleta⁷, Pablo Rojo⁷, EMPIRICAL Clinical Trial Group

Table 1: Baseline patient characteristics

	n = 310
Demographic	
Age (months, median)	4.5 (IQR, 3.2-7.3)
Sex (female)	50%
Clinical	
Chest indrawing	284 (92%)
Oxygen saturation <90%	199 (64%)
Lethargic or unconscious	80 (26%)
Unable to drink/breastfeed	97 (32%)
Severe malnutrition	226 (73%)
Laboratory	
HIV viral load (median)	6.3 logs cp/mL (IQR, 5.8-7.0)
CD4% (median)	14.4% (IQR, 9.9-21.6)
White blood cell count (median)	12.9 (IQR, 8.7-18.7)
Hemoglobin (median)	9.2 (IQR, 8.1-10.2)
ALT (median)	21 (IQR, 14-37)

Figure 3: Kaplan-Meier survival analysis



The probability of 15-day and 12-month survival was 71% and 50%, respectively

Pasanduca A, CROI 2023

Adequate DTG exposure in infants on rifampicin treatment receiving twice-daily DTG

Tom G. Jacobs¹, Vivian Mumbiro², Uneisse Cassia³, Damalie Nalwanga⁴, Kevin Zimba⁵, Sara Domínguez-Rodríguez⁶, Constantine Mutata², W. Chris Buck⁷, Chishala Chabala⁵, Victor Musiime⁴, Mutsa Bwakura-Dangarembizi², Cinta Moraleda⁶, David M. Burger¹, Pablo Rojo⁶, Angela Colbers¹, on behalf of the EMPIRICAL clinical trial group

¹Radboud University Medical Center, Nijmegen, The Netherlands, ²University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe, ³Universidade Eduardo Mondlane, Maputo, Mozambique, ⁴Makerere University, Kampala, Uganda, ⁵University Teaching Hospital, Lusaka, Zambia, ⁶Fundación para la Investigación Biomédica del Hospital Universitario 12 de Octubre (imas12), Madrid, Spain, ⁷University of California Los Angeles, Maputo, Mozambique

Demographics		Control arm (n=6)	Rifampicin arm (n=21)
Male/Female		3/3	13/8
Weight (kg)		5.9 (5.8-8.0)	6.4 (4.9-7.1)
Weight band	3-6kg	2	11
	6-10kg	4	10
Age (months)		7.4 (6.4-8.8)	6.6 (5.6-10.5)
DTG dose mg/kg		1.86 (1.09-2.36)	1.33 (1.00-2.08)
Reported: Median(IQR)			

PK parameter	Control arm (n=6)	Rifampicin arm (n=21)	Geometric mean ratio
C _{trough} (mg/L)	1.11 (46)	1.05 (82)	1.05 (90% CI 0.69 - 1.60)
AUC _{0-12h} (h*mg/L)	54.4 (39)	49.7 (70)	1.09 (90% CI 0.76 - 1.57)
C _{max} (mg/L)	3.86 (38)	3.36 (65)	1.15 (90% CI 0.81 - 1.63)
Reported: Geometric mean (CV%)			

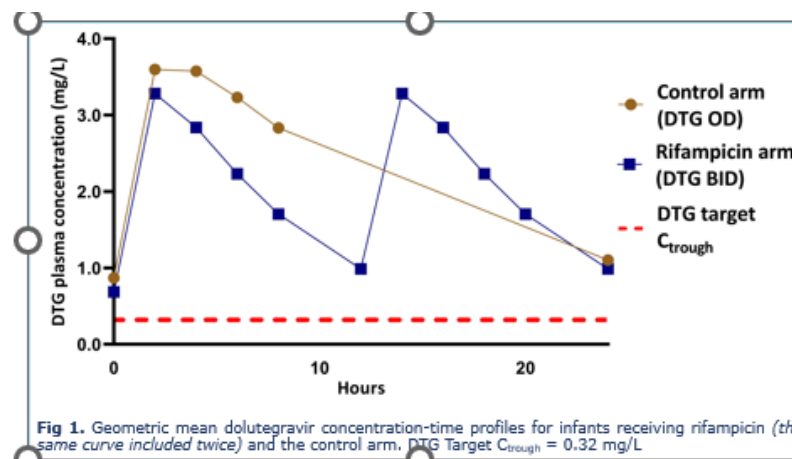
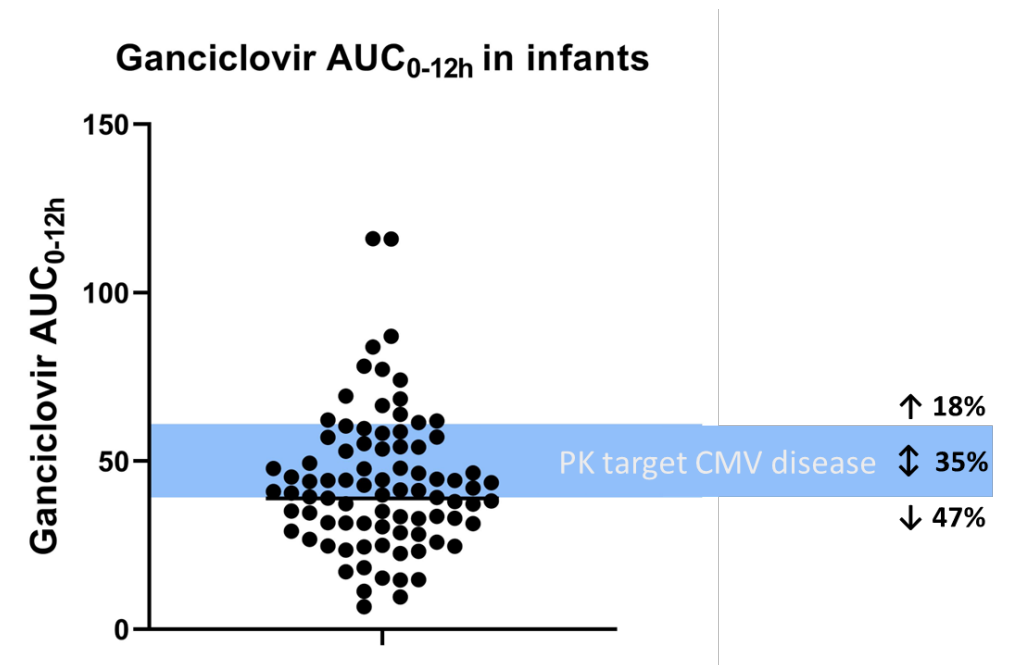


Fig 1. Geometric mean dolutegravir concentration-time profiles for infants receiving rifampicin (the same curve included twice) and the control arm. DTG Target C_{trough} = 0.32 mg/L



PK3, VALGANCICLOVIR LEVELS

- Valganciclovir reconstituted syrup was given at 16mg/kg/dose every 12 hours, and pharmacokinetic sampling was done 2 and 5 hours post-administration on day 3 of enrolment after at least 3 doses.
- The geometric mean AUC and proportion of subjects within the pharmacokinetic target for CMV treatment (AUC_{0-12h} 40-60 h*mg/L) were determined.



THANKS!

